

REMARKS

Claims 90-127 are pending in the present application. Claims 1-89 have been cancelled without prejudice or disclaimer. Claims 112-127 have been newly added. Claims 1-89 have been cancelled without prejudice or disclaimer. Claims 90, 92-94 and 97-99 have been amended.

Applicants, by canceling or amending any claims herein, make no admission as to the validity of any rejection made by the Examiner against any of these claims. Applicants reserve the right to reassert any of the claims canceled herein or the original claim scope of any claim amended herein, in a continuing application.

Claims 90 and 97 have been amended to remove the recitation of "wherein upon thawing the thawed viable cartilage comprises more than 50% viable chondrocytes." Claims 98 and 99 have been amended to clarify that the warming refers to warming the receptacle containing the frozen viable cartilage and the cryopreservation solution from the initial temperature to the intermediate temperature. Claims 90, 92 and 97 have been amended to correct grammatical errors. Claim 94 has been amended to correct dependency. Support for the amendment to claims 90, 92-94 and 97-99 can be found throughout the specification and claims as originally filed.

New claim 112 is, in general, directed to a method of thawing cartilage. New claim 113 is, in general, directed to a method of freezing and thawing cartilage. New dependent claims 114-127 recite further elements relating to the independent claims from which each depend from. New claims 112-127 find support throughout the specification, examples and claims as originally filed.

No new matter has been added.

In view of the following, further and favorable consideration is respectfully requested.

I. At page 3 of the Official Action, claims 93 (92), 94 and 97-106 have been rejected under 35 USC § 112.

The Examiner asserts that claims 93, 94 and 97-106 are indefinite for the reasons set forth in the Official Action.

From the outset, Applicants note that it appears that the Examiner meant to reject claim 92 and not claim 93. For the purposes of this response, Applicants will address this rejection as including claim 92 and not claim 93.

In view of the following, Applicants respectfully traverse the rejection of claims 92, 94 and 97-106.

Applicants submit that rejection of each of claims 92, 94 and 97-106 have been obviated by the amendments to claims 92, 94 and 97-99. In this regard, Applicants note that claims 92 and 97 have been amended to correct grammatical errors. Claim 94 has been amended to correct dependency. Claims 98 and 99 have been amended to clarify that the warming refers to warming the receptacle containing the frozen viable cartilage and the cryopreservation solution from the initial temperature to the intermediate temperature.

In view of the foregoing, Applicants submit that claims 92, 94 and 97-106 are clear and definite within the meaning of 35 USC § 112, second paragraph. Accordingly, reconsideration and withdrawal of this rejection is respectfully submitted.

II. At page 10 of the Official Action, claims 90-111 have been rejected under 35 USC §103(a) as being unpatentable over Schachar et al. (of record) in view of various combinations of Sigma Product Information Sheet for Dimethyl sulfoxide ("Sigma"), Kushibe et al. (of record), Brockbank (US Patent No. 5,131,850), Arav (US Patent No. 5,873,254), Pegg et al. (of record)

The Examiner asserts that it would have been obvious to modify the method of freezing according to Schachar et al., i.e., at a temperature of -80°, with the various teachings of the several references.

In view of the following, this rejection is respectfully traversed.

To establish a *prima facie* case of obviousness, the PTO must satisfy three requirements. First, as the U.S. Supreme Court held in *KSR International Co. v. Teleflex Inc. et al.*, 550 U.S. 398 (2007), "a court must ask whether the improvement is more than the predictable use of prior art elements according to their established functions. ...it [may] be necessary for a court to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue. ...it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does... because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known." (*KSR, supra*) Second, the proposed modification of the prior art must have had a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention

was made. *Amgen Inc. v. Chugai Pharm. Co.*, 18 USPQ2d 1016, 1023 (Fed. Cir. 1991). Lastly, the prior art references must teach or suggest all the limitations of the claims. *In re Wilson*, 165 USPQ 494, 496 (C.C.P.A. 1970).

Regarding motivation to modify properly combined references, **MPEP 2143** states that where the prior art conflicts, all teachings must be considered and that the fact that references can be combined or modified is not sufficient to establish *prima facie* obviousness. **MPEP 2143** further states that there must be some suggestion or motivation to modify the references, and there must be a reasonable expectation of success.

MPEP 2143.01 states that a proposed modification cannot render the prior art unsatisfactory for its intended purpose. If it does, then there is no suggestion or motivation to make the proposed modification. Further, the proposed modification cannot change the principle operation of a reference.

Applicants respectfully submit that there is no motivation to modify the method described by Schachar et al. to arrive at the presently claimed subject matter because a skilled artisan would not have a reasonable expectation of success. In addition, the principle mode of operation described by Schachar et al., i.e., cooling by controlled cooling, would be destroyed.

Claims 90-111 are generally directed to methods of generating frozen viable cartilage and methods of thawing methods of thawing frozen viable cartilage.

In contrast to the presently pending claims, Schachar et al. describes a method for freezing cartilage by immersing the cartilage in DMSO, cooling to -40°C at a cooling rate of -1°C/min and then storing the frozen cartilage at -80°C

for as long as 4 weeks. See Schachar et al., for example, at *Treatment groups* on page 911, right column.

Unlike the presently claimed subject matter, Schachar et al. do not teach or suggest storing at a temperature equal to or below -130°C , as recited in present claim 90. In fact, Schachar et al. only describe storing at significantly higher temperatures of at least -80°C . In addition, Schachar et al. do not teach or suggest directional cooling as presently claimed, i.e., moving the receptacle on a temperature gradient. Further, Schachar et al. indicate that cryoprotection and controlled cooling are **required** to increase the viability of cartilage. See Schachar et al., for example, at the *Abstract* and *Discussion* on page 918, left column.

As appreciated by those versed in the art, chondrocyte viability is crucial for the longevity of grafted cartilage in order to improve the viability of post thawed cartilage after transplantation. Thus, the difference between the viability provided by Shachar et al. and that provided by the presently described subject matter is of great significance as it allows the post thawed cartilage to survive in the body and serve its desired purpose significantly longer than the post thawed cartilage provided by Schachar et al.

The high viability of the present post thawed cartilage is achieved by directional freezing of the cartilage. "Freezing can be done using any apparatus or method that will allow directional freezing of the cartilage, such as the Multi Thermal Gradient (MTG) freezing apparatus (IMT, Israel) that was used above." See the specification at page 25, lines 18-20. The directional freezing also allows the long term storage at -130°C and below (for even months, see page 26, lines 2-3), which is not possible with storage at -80°C . Directional freezing forces ice

crystals to slowly grow into the lacunas within the ECM without causing fractures of the lacunas and as such facilitates the aforementioned long term storage and high viability of the present post thawed cartilage.

As discussed in the previously filed response and amendment, the presently claimed subject matter provides higher post thawing viability of the frozen cartilage than the method of Schachar et al. As shown in present Table 1, the viability of the cartilage in accordance with the presently described subject matter is relatively high. Applicants note that this higher viability as compared to the viability obtained by prior cryopreservation techniques, such as that suggested by Schachar et al., is unexpected.

Applicants respectfully submit that modifying the controlled freezing process as suggested by the Examiner, i.e., to a storage temperature of -130°C or cooler, would not result far less viable chondrocytes than the presently claimed method.

Further, Applicants submit that modifying Schachar et al. to utilize directional cooling would destroy the principle mode of operation described by Schachar et al. In this regard, Applicants note that whereas the presently claimed subject matter is directed to directional cooling Schachar et al. require controlled cooling. Applicants respectfully submit that changing the cooling method in Schachar et al. to directional cooling as well as changing temperature variables to those claimed would destroy the mode of operation required by Schachar et al., that is, controlled cooling.

In view of the foregoing, Applicants submit that nothing in Schacher et al., taken alone or in combination with the cited references, render the present subject matter obvious within the meaning of 35 USC § 103. Accordingly, reconsideration and withdrawal of this rejection is respectfully submitted.

III. New Claims 112-127

New independent claims 112 and 113 are directed to a method of freezing cartilage and method freezing and thawing cartilage. Each of new claims 112 and 113 recite “placing the thawed viable cartilage in a buffered physiological solution comprising a non-cell membrane permeable biocompatible sugar, polyol or other organic solute.” Claims 114-119 further characterize the buffered physiological solution in claims 112 and 113. Claims 120-123 depend from claims 90, 97, 112 and 113, respectively. Each of claims 120-123 recite “wherein upon thawing the thawed viable cartilage comprises more than 65% viable chondrocytes.” Claims 124-127 also depend from claims 90, 97, 112 and 113, respectively. Each of claims 124-127 recite “wherein the receptacle further contains bone.”

Applicants respectfully submit that new claims 112-127 are each novel and non-obvious. Accordingly, Applicants respectfully request an indication that all of the pending claims are in condition for allowance.

CONCLUSION

In view of the foregoing, Applicant submits that the application is in condition for immediate allowance. The Examiner is invited to contact the undersigned attorney if it is believed that such contact will expedite the prosecution of the application.

In the event this paper is not timely filed, Applicants petition for an appropriate extension of time. Please charge any fee deficiency or credit any overpayment to Deposit Account No. 14-0112.

Respectfully submitted,

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